General

Guideline Title

Extra-corporeal photopheresis in the management of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants: recommendations.

Bibliographic Source(s)

Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT, Stem Cell Transplant Steering Committee. Extra-corporeal photopheresis in the management of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants: recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2013 Aug 29. 29 p. (Recommendation report; no. SCT-5). [35 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Extra-corporeal Photopheresis (ECP) in the Management of Graft-versus-Host Disease (GVHD)

- ECP is an acceptable therapy for the treatment of steroid-dependent/refractory acute GVHD in adult and paediatric patients.
- ECP is an effective therapy for the treatment of steroid-dependent/refractory chronic GVHD in adult and paediatric patients.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Graft-versus-host disease (GVHD)

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Allergy and Immunology

Family Practice

Hematology

Internal Medicine

Oncology

Pediatrics

Intended Users

Physicians

Guideline Objective(s)

To determine whether there is a benefit associated with the use of extra-corporeal photopheresis (ECP) compared with other treatment options for patients who have received an allogeneic transplant and are experiencing graft-versus-host disease (GVHD) if response rate, survival, or improvement in symptoms are the outcomes of interest

Target Population

Adult and paediatric patients who have received an allogeneic transplant and are experiencing graft-versus-host disease (GVHD)

Interventions and Practices Considered

Extra-corporeal photopheresis (ECP) in the management of graft-versus-host disease (GVHD)

Major Outcomes Considered

- Response rate (skin response, extracutaneous response)
- Survival
- Improvement in symptoms
- Adverse effects

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The MEDLINE (Ovid) (1995 through July Week 1 2012) database was searched on July 17, 2012 and updated on August 14, 2013. The search strategy for MEDLINE is shown in Appendix 1 of the original guideline. Search terms for stem cell transplantation, bone marrow transplantation, and peripheral blood stem cell transplantation were combined, and articles that also included graft-versus-host disease outcomes where photopheresis was administered were retained. As it was expected that there would be little indexed evidence, no restrictions were made based on publication date.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full-report articles or published meeting abstracts of:

1. Studies that reported on outcomes of extra-corporeal photopheresis administered for either acute or chronic graft-versus-host disease for patients of all ages following allogeneic stem cell transplantation
2. One of the following publication types or study designs: practice guidelines with systematic review, systematic reviews (with meta-analyses), systematic reviews (without meta-analyses), randomized phase III trials, randomized phase II trials, or other comparative studies.

No specific outcomes were required, as long as the study met the two points above.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, due to financial considerations for translation.
3. Reported on fewer than five patients.

Number of Source Documents

A total of 18 papers were retained.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software (RevMan 4.2) available from the Cochrane Collaboration. For time-to-event outcomes, hazard ratios (HRs), rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in (the software used) would be used.

Statistical heterogeneity would be calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

Assessment of Study Quality

For systematic reviews that would be used as the sole evidence base for our recommendations, the Assessment of Multiple Systematic Reviews (AMSTAR) tool would be used to assess quality. For Clinical Practice Guidelines, the Assessment of Guidelines Research and Evaluation (AGREE) II instrument would be used to assess quality. However, because of the time and effort necessary to properly implement the AGREE II instrument, it would be used only if adaptation of the recommendations was considered feasible by the working group given the nature and coverage of the guideline and an informal assessment of the guideline's methods. Where recommendations from clinical practice guidelines (CPGs) were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any meta-analysis would be assessed for quality using similar criteria as used for randomized controlled trials (RCTs), where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This recommendation report, produced by the Program in Evidence-based Care (PEBC) and the Stem Cell Transplantation Steering Committee (the Committee) of Cancer Care Ontario (CCO), was developed through a systematic review of the available evidence and the interpretation of that evidence by clinical experts to develop recommendations. A working group was formed of members of the Committee to develop the report.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by a consensus report based on a systematic review, randomized controlled trials, a non-randomized controlled trial, prospective cohort studies, retrospective cohort studies, a clinical practice guideline, comparative and non-comparative studies, and case series.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- One study detected a statistically significant difference in response rates in favour of extra-corporeal photopheresis (ECP) over conventional corticosteroid treatment (40% vs. 10%; p=0.002). Similarly, another study reported a significant increase in the overall response rate associated with EPC when compared to conventional treatment (26% vs. 8%; p=0.04).
- One study reported on quality-of-life outcomes, with a significant benefit being detected with ECP treatment compared with conventional treatment (ECP: 19% vs. control: 2.5%; p=0.01).
- A randomized controlled trial (RCT) reported on total skin scores, eye, oral, and joint changes associated with graft-versus-host disease (GVHD), and adverse events. Significant differences were only detected in eye GVHD, which showed an improvement associated with ECP compared with conventional treatment (ECP: 30% vs. control: 7%; p=0.04).
- A case series reported on changes from baseline scores after 6 months for cutaneous, hepatic, pulmonary, mucosal, and neuromuscular chronic GVHD (cGVHD), and significant improvements were detected for cutaneous cGVHD scores only (baseline: 89% [skin median score: 131, 132] vs. 6 months: 52% [skin median score: 61]; p=0.003).

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Extra-corporeal photopheresis (ECP) is currently a covered therapy in Ontario for patients with steroid refractory graft-versus-host disease (GVHD) who meet certain eligibility criteria.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the

report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Aug 29

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Stem Cell Transplant Steering Committee

Composition of Group That Authored the Guideline

Primary Authors: C. Bredeson (*Lead Author*), R.B. Rumble, N.P. Varela, J. Kuruvilla, C.T. Kouroukis

Financial Disclosures/Conflicts of Interest

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic. The lead author reported a potential conflict because if photopheresis were to become a widely funded procedure, his income could potentially increase by more than $10,000. The remaining authors reported no conflicts of interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Extra-corporeal photopheresis in the management of graft-versus-host disease in patients who have received allogeneic blood or bone marrow transplants: recommendations. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2013 Aug 29. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.

- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2011. 15 p. Electronic copies: Available in PDF from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 16, 2013.

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